Executive deficits, not processing speed relates to abnormalities in distinct prefrontal tracts in amyotrophic lateral sclerosis

Executive deficits, not processing speed relates to abnormalities in distinct prefrontal tracts in ALS

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Summary

Cognitive impairment in amyotrophic lateral sclerosis (ALS) is characterized by deficits on tests of executive functions, however, the contribution of abnormal processing speed is unknown. Previous methodology is confounded by tasks which depend on motor speed in patients with physical disability. Structural and functional MRI studies have revealed multi-system cerebral involvement, with evidence of reduced white matter volume and integrity in predominant frontotemporal regions. The current study has two aims. Firstly, to investigate whether cognitive impairments in ALS are due to executive dysfunction or slowed processing speed using methodology which accommodates motor disability. This is achieved using a dual task paradigm and tasks which manipulate stimulus presentation times that do not rely on response motor speed. Secondly, to identify relationships between specific cognitive impairments and the integrity of distinct white matter tracts. Thirty ALS patients and thirty age- and education-matched controls were administered an experimental dual task procedure which combined a visual inspection time task and digit recall. In addition, measures of executive functions (including letter fluency) and processing speed (visual inspection time and rapid serial letter identification) were administered. Integrity of white matter tracts was determined using region-of-interest analyses of diffusion tensor MRI data. ALS patients did not show impairments on either tests of processing speed, but executive deficits were revealed once visual inspection time was combined with digit recall (dual task) and letter fluency. In addition to the corticospinal tracts, significant differences in fractional anisotropy (FA) and mean diffusivity ($\langle D \rangle$) were found between groups in a number of prefrontal and temporal white matter tracts including the anterior cingulate, anterior thalamic radiation, uncinate fasciculus and hippocampal portion of the cingulum bundles. Significant differences also emerged in the anterior corona radiata as well white matter underlying the superior, medial and inferior frontal gyri, and the temporal gyri. Dual task performance significantly correlated with FA measures in the middle frontal gyrus white matter and anterior corona radiata. Letter fluency indices significantly correlated with FA measures of the inferior frontal gyrus white matter and corpus callosum, in addition to the corticospinal tracts

and ⟨D⟩ measures in the superior frontal gyrus white matter. The current study demonstrates that cognitive impairment in ALS is not due to generic slowing of processing speed. Moreover different executive deficits are related to distinct prefrontal tract involvement in ALS, with dual task impairment associated with dorsolateral prefrontal dysfunction while letter fluency showed greater dependence on inferolateral prefrontal dysfunction.

Key words: Amyotrophic lateral sclerosis; diffusion tensor imaging, dual task, cognition.

Total Word Count in Text 6924

Introduction

Cognitive profile of ALS

Amyotrophic lateral sclerosis (ALS) is characterised by progressive degeneration of the upper motor neurons of the corticospinal tract, and the lower motor neurons of the brain stem and spinal cord. However, it is now well recognised that ALS is a multi-system disorder as changes in extra-motor areas of the cortex have been consistently observed (Kew *et al.,* 1993a; Abrahams *et al.,* 1996; Geser *et al.,* 2008). A relationship exists between ALS and frontotemporal dementia (FTD) with 5 – 15% of ALS patients developing an FTD syndrome, predominantly a behavioural variant associated with TDP-43 pathology (Neary *et al.,* 2000; Geser *et al.,* 2009). Moreover, a larger proportion (~35%) of non-demented ALS patients present with specific cognitive impairment (e.g Ringholz *et al.,* 2005; Phukan *et al.* 2012) implicating a spectrum of cognitive change between FTD and ALS, and with sub-clinical FTD symptoms in a significant number of cases (Girardi, MacPherson & Abrahams, 2011; Abrahams 2012). Recent genetic studies have revealed a hexanucleotide repeat expansion in C9rof72 which accounts for 41% of familial and 5% of sporadic cases (Byrne et al. 2012). ALS with the mutation have a distinct phenotype with an increase in FTD. Non-demented ALS patients with the expansion display similar levels of executive dysfunction but less non-executive cognitive dysfunction than those without the expansion (Byrne et al. 2012).

In non-demented ALS patients, the most commonly reported deficits are in tests of executive functioning (Kew *et al.,* 1997; Abrahams *et al.,* 2000; Lomen-Hoerth *et al.,* 2003); the most striking and consistent impairment are on tests of letter (phonemic) fluency (Raaphorst *et al.,* 2010), which remain even when individual variations in motor dysfunction and speed are controlled for (Abrahams *et al.,* 2000). The tasks, require intrinsic generation of responses in the absence of environmental cues (Frith *et al.,* 1991), and are thought to include executive processes of initiation, strategy formation, sustained attention, set-shifting, inhibition and working memory (Troyer *et al.,* 1997; Azuma, 2004; Abrahams *et al.,* 2000; Rende *et al.,* 2002). ALS patients have also been shown

to have deficits on tasks in which information is manipulated rather than just held within working memory such as the Reverse Digit Span (Rakowicz *et al.,* 1998; Hanagasi *et al.,* 2002; Robinson *et al.,* 2009), and the Paced Auditory Serial Addition Test (Moretti *et al.,* 2002). In terms of Baddeley's (2000) model of working memory, it is postulated that the 'central executive' is impaired in ALS (Abrahams et al. 2000), an attentional control system which coordinates independent short term memory slave systems (the phonologic loop for auditory information and the visuo-spatial sketch pad for visual information) by allocating resources and directing attention in order to maintain and manipulate information. Dual-task paradigms in which a participant performs a visual and auditory task concurrently are commonly used to investigate this particular function (Cocchini *et al.,* 2002). Dual-tasking has been shown to be impaired in patients with FTD (Perry & Hodges, 2000; Sebastian & Hernandez-Gil, 2010), and a deficit was reported by one study in ALS (Schreiber *et al.,* 2005), although the performance measurement in this study was reaction time (motor speed) which may falsely exaggerate impairment in ALS due to physical disability.

Processing speed also plays an important role in fluency tasks. Performance in measures such as the Digit Symbol Substitution Test and Letter Comparison Task have been found to be strong predictors of fluency performance in populations with traumatic brain injury (Bittner & Crowe, 2007), Parkinson's disease (McDowd *et al.,* 2011), and normal ageing (Bryan *et al.,* 1997). Moreover, processing speed is thought to be a major deficit in other disorders characterized by white matter abnormalities, such as Multiple Sclerosis (Huijbregts *et al.,* 2006; Dineen *et al.,* 2009). Indeed, ALS patients have been shown to be impaired on the Symbol Digit Modalities Test (Mezzapesa *et al.,* 2007). However processing speed is inherently difficult to measure in populations with motor dysfunction due to the reliance of most tasks on timed motor responses, or reaction times (e.g. Digit-Symbol Substitution Test, Wechsler, 1981; Digit-Digit task, Salthouse, 1994a) and measurement using standardized psychomotor tests will once again be confounded by motor disability.

Neural correlates of cognitive impairment in ALS

Evidence for a frontotemporal syndrome in ALS comes from brain imaging data (Tsermentseli *et al.* 2012). Analyses of structural MRI scans of non-demented ALS patients employing manual and automated volumetric techniques have reported reduced grey matter volume in the superior, medial, mid frontal gyri and anterior cingulate (Ellis *et al.,* 2001; Chang *et al.,* 2005; Kassubek *et al.,* 2005; Grosskreutz *et al.,* 2006; Lillo et al. 2012), as well as the inferior frontal gyri, superior temporal gyri and temporal poles (Chang *et al.,* 2005), although not consistently (Kiernan & Hudson, 1994; Abrahams *et al.,* 2005). Abnormalities have also been exhibited in extra-motor white matter underlying anterior frontal cortex (Kiernan & Hudson, 1994; Kassubek *et al.,* 2005), frontotemporal association fibres implicating the superior longitudinal fasciculus, cingulum, and fronto-occipital fasciculus (Abrahams *et al.,* 2005), as well as the corpus callosum (Kassubek *et al.,* 2005; Abrahams *et al.,* 2005). The recent application of diffusion tensor MRI (DTI) has proved useful in monitoring white matter integrity and disease progression in the corticospinal tract (Agosta *et al.,* 2010; Bastin *et al.*, 2013), and detected abnormalities in the corpus callosum (Filippini *et al.,* 2010; Lillo et al. 2012) and uncinate fasciculus (Sato *et al.,* 2010).

Despite these advances in brain imaging, relatively few studies have directly investigated the relationship between localized cerebral changes and patients' cognitive profile. Functional imaging studies provide evidence to suggest that the neural correlates of impaired fluency performance in ALS are predominantly prefrontal (Tsermentseli et al., 2012). ALS patients with impaired verbal fluency scores have shown reduced cerebral blood flow in prefrontal regions including dorsolateral prefrontal cortex and anterior cingulate in letter fluency activation paradigms in PET (Abrahams *et al.,* 1996) and functional MRI (Abrahams *et al.,* 2004). Cerebral blood flow reductions were shown in comparison to matched controls, and to patients with intact fluency performance, illustrating the degree of heterogeneity within ALS patient cohorts. Moreover, a recent functional MRI study examined response inhibition in ALS and found evidence of altered activation patterns, relative to

controls in prefrontal regions including left superior gyrus, left anterior cingulum, and left medial frontal gyrus (Goldstein *et al.,* 2011). Associations between cognitive and behaviour change and structural MRI has been investigated in a recent study in which patients with evidence of cognitive impairment (deficits across two tests of executive functions) and or behavior change (two non-overlapping behavioural features) showed greater grey matter atrophy than ALS patients without such symptoms using automated voxel based analyses (Mioshi et al. 2013). Atrophy was evident across motor and somatosensory cortical regions which extended into adjacent areas including the superior frontal and parietal gyri. Association with white matter changes has been shown in one study in which patients with impaired verbal fluency had extensive volumetric reductions in frontotemporal white matter regions, whereas those ALS patients who were unimpaired in verbal fluency showed less changes, suggesting that these white matter structures may underpin poor task performance (Abrahams *et al.,* 2005). To our knowledge, only one study has investigated the relationship between DTI metrics and cognitive functioning in ALS (Sarro *et al.,* 2011). In that study, performance on tests of executive functioning (including verbal fluency) were correlated with reduced white matter integrity in the corpus callosum, cingulum, inferior longitudinal fasciculus and uncinate fasciculus, although fluency measures were not adapted to control for motor dysfunction.

The current study therefore aimed to (i) dissociate impairments in executive functions from slowed processing speed in ALS using tasks which account for motor dysfunction and (ii) gain an understanding of the changes in white matter integrity in distinct pathways which may be associated with any cognitive abnormality. The current investigation employed tasks that do not utilize reaction time as their output measure but rather manipulate stimuli presentation times in order to estimate processing speed. Two paradigms were devised; one for meaningful and one for abstract visual information. Similar paradigms of abstract visual information have been used to investigate processing speed in cognitive ageing and Parkinson's disease (Edmonds *et al.,* 2008; Johnson *et*

*al.,*2004). Moreover, in line with the recent emphasis of linguistic impairment in ALS (Taylor *et al.* 2012; see Abrahams 2012 for comment), the processing speed of linguistic material was also investigated using rapid serial visual letter identification. This methodology is analogous to inspection time paradigms which have been consistently used to provide measures of perceptual speed (Schneider & Shiffrin, 1977; Broadbent & Broadbent, 1987). Executive functioning was investigated by way of a dual-task paradigm; which employed a processing speed task and a working memory task as its sub-tasks and utilized a preload methodology to minimize demands on the motor system. A participant's performance level on each sub-task was titrated to ensure that each task was of equal difficulty prior to undertaking them together. Similar paradigms have been used to investigate dual-task abilities across the lifespan (Cocchini *et al.,* 2002; Anderson *et al.,* 2011), and allow processing speed and working memory to be investigated independently and under dual-task conditions.

Materials and methods

Participants

The patient group consisted of thirty people with ALS, recruited from regional ALS services at the following NHS sites: Western General Hospital, Edinburgh; Southern General Hospital, Glasgow; and Ninewells Hospital, Dundee, Scotland and from the MND register for Scotland, University of Edinburgh. All had clinical and electrophysiological evidence of combined upper and lower motor neurone involvement and fulfilled the revised El Escorial criteria for clinically definite or probable ALS (Brooks *et al.,* 1998). Twenty-six patients had sporadic ALS and four had a history of suspected ALS in a first degree relative. Genetic screening was available on 11 of the 30 patients, of whom 2 were found to be positive for C9orf72, neither of whom had a family history. Ten patients had bulbar onset, eleven had upper limb onset, and 9 had lower limb onset. Exclusion criteria for patients included the presence of another neurological disorder, history of psychiatric disorder, or high

cardiovascular risk factors. No patient had evidence of dementia in clinical notes or on initial discussion, although one patient was subsequently found to fulfil the criteria for possible behavioural variant FTD (Rascovsky *et al.,* 2011) following a detailed interview with a caregiver. Disease progression and severity was assessed in patients by administering the *ALS Functional Rating Scale-Revised* (ALSFRS-R; Cedarbaum *et al.,* 1999). Respiratory functioning was assessed with Forced Vital Capacity predicted/expected ratio and the *Epworth Sleepiness Scale* (Johns, 1991). Thirty age- and education-matched healthy controls were recruited from the University of Edinburgh Psychology Department's Volunteer Participant Panel, or from spouses of patients. All participants had normal hearing and corrected vision and did not have significant neurological or psychiatric comorbidity. This study was approved by NHS Scotland Research Ethics Committee and the Department of Psychology, University of Edinburgh and undertaken in accord with the Declaration of Helsinki.

Background Assessment

The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) was used to estimate premorbid intelligence. The *Hospital Anxiety and Depression Scale* (HADS; Zigmond & Snaith, 1983) was used to exclude the possibility that an abnormal cognitive profile might be related to emotional state. The question "I feel as if I am slowed down" has exaggerated salience to ALS patients who experience motor dysfunction and was therefore not included in the score (Abrahams *et al.,* 2005). The *Graded Naming Test* (GNT; McKenna & Warrington, 1983) was employed to provide a measure of confrontation naming. The Digit Span, Spatial Span and Logical Memory subtests of the Wechsler Memory Scale—III (WMS−III; Wechsler, 1999b) were used to assess verbal working memory, spatial working memory, and immediate and delayed recall of verbal information respectively. Executive functioning was assessed by two tests: 1. The *Brixton Spatial Anticipation Test* (Burgess & Shallice, 1997) is a commonly used measure of executive functioning which requires minimal motor output and assesses rule detection and set shifting. 2. The Written Letter Fluency Test and Spoken Letter

Fluency Test were employed to assess initiation, strategy formation, set-shifting and monitoring; both fluency tests accommodate for physical disability by producing a fluency index (Abrahams *et al.,* 2000) which controls for speaking/writing time and produces a measure of thinking time.

Experimental Cognitive Testing

Processing Speed

Visual Inspection Time (VIT, adapted from Edmonds *et al.,* 2008): Participants were required to make a forced choice decision regarding an abstract visual stimulus presented briefly on a computer screen. The target stimulus was a simple geometric figure with a clearly elongated "tail" on either the left or right side. Following brief presentation participants were required to indicate whether they saw a longer tail on the left or right side. During the test procedure, participants did not receive feedback, and the duration time of the stimulus was manipulated in a fixed pseudorandom order at durations of 150, 125, 102, 85, 68, 51, 34 and 17 ms. A total of 80 trials were completed, 10 at each stimulus duration.

(Insert Figure 1 about here)

Rapid Serial Letter Identification (RSLI) task: In this task, adapted from Hoffman (1978), participants were presented with a sequence of six consecutive letters. Five of the letters within the stream were black, and one, the target, was red which was presented in random positions. Participants were required to identify the target letter verbally. Processing speed was investigated by manipulating the duration of the presentation of the letter stimuli in any one sequence in a fixed pseudorandom order (150, 125, 102, 85, 68, 51, 34 or 17 ms). There were 40 trials in total, 5 at each duration, and the response accuracy was recorded.

(Insert Figure 2 about here)

Executive functioning: Dual Task Paradigm

The dual task paradigm consisted of combining the VIT (described above) with Delayed Digit Recall (DDR), both of which were titrated to an individual's abilities. A similar paradigm has been used to investigate dual task ability, without the confounds of reaction time based tasks, in children and older adults (Anderson *et al.,* 2011). The dual task employed a preload paradigm (Cocchini *et al.,* 2002) as typical concurrent dual task paradigms are likely to put high demands on response selection and initiation and thus result in interference, especially in populations with motor difficulties. All participants completed the dual task procedure in the same order as follows:

1. Individual Ability Levels

a) DDR Individual level: The participant's individual DDR level was determined, by presenting them with increasing sequences of numbers to recall from two items with three trials at each length. Participants were presented with digits aurally at a rate of one per second, and asked to recall them after a fifteen second delay. If 2 out of 3 trials were completed accurately then the number of items per sequence was increased. DDR level was taken as the maximum number of items that were recalled accurately in at least 2 out of 3 trials.

b) VIT Individual level: Participants individual VIT level was determined by presenting them with stimuli at increasingly shorter durations (150, 125, 102, 85, 68, 51, 34 and 17 ms). Six VIT trials were presented at each stimulus duration – if participants accurately responded to five, they moved on to the next shortest duration. The stimulus duration time at which participants failed to reach the accuracy criterion (5 out of 6 trials correct) was taken as their VIT level.

2. Single Tasks

a) DDR Single Task: This consisted of 8 trials made from digit sequences of one less than their DDR level – this procedure was adopted following a pilot dual task study which revealed that performing the dual task at maximum ability was overly difficult. The total number of digits correctly recalled was converted to a percentage of the total number of digits presented to give DDR single task performance (% correct = No. of Digits recalled/Total No. of Digits).

b) VIT Single Task: This consisted of 8, 15s blocks of VIT trials with durations one step below their VIT level. The total number of correct responses was converted to a percentage of total number of trials to give VIT single task performance (% correct = No. correct/Total No. of Trials).

3. Dual Task (DDR and VIT)

Participants completed 8 trials which consisted of first presentation of the digit sequence, followed immediately by the VIT trials (15s) and subsequent recall of the digits. Percentage correct (as described above) was calculated for the DDR and VIT dual task respectively. Finally, a measure of dual task cost for each task was calculated by comparing performance in the single to dual task conditions: Dual Task Cost = [(Dual task % correct – Single task % correct) x100]/ Single task % correct.

The average of the two component tasks is a better representation of performance as it controls for strategic prioritizing of one task over the other, thus finally combined average accuracy scores were computed for single task performance, dual task performance, and dual task cost.

(Inset Figure 3 about here)

MRI Acquisition

All MRI data were acquired using a GE Signa Horizon HDxt 1.5 T clinical scanner (General Electric, Milwaukee, WI, USA) equipped with a self-shielding gradient set (33 mT/m maximum gradient strength) and manufacturer supplied 8-channel phased-array head coil. The diffusion MRI protocol consisted of 7 T_2-weighted (b ~ 0 s/mm^2) and sets of diffusion-weighted (b = 1000 s/mm^2) whole brain single-shot spin-echo echo-planar imaging (EPI) volumes acquired with diffusion encoding gradients applied in 64 non-collinear directions (Jones *et al.*, 2002). The acquisition parameters were: field-of-view 256 × 256 mm; imaging matrix 128 × 128; and 72 × 2 mm thick contiguous axial slice locations giving 2 mm isotropic voxels. The repetition and echo times for the single-shot spin-echo EPI sequence were 16.5 s and 98.3 ms respectively. The examination took approximately 20 minutes.

MRI Analyses

Regions of Interest

Semi-automated region-of-interest (ROI) analysis was performed using 'in-house' software written in MATLAB (The MathWorks, Natick, MA, USA) that allowed multiple small square ROIs to be placed on the T_2-weighted EPI volumes and then overlaid on the co-registered mean diffusivity ($\langle D \rangle$) and fractional anisotropy (FA) maps either by hand or automatically using locations defined in Montreal Neurological Institute (MNI; http://www.bic.mni.mcgill.ca) standard space. In the latter, the software allows the user to interactively move ROIs if standard to native space registration errors cause white matter ROIs to be placed over cerebrospinal fluid (CSF) or grey matter structures.

The procedure for obtaining $\langle D \rangle$ and FA values for each ROI was as follows. First, MNI coordinates were defined in standard space for each ROI using the ICBM-DTI-81 white matter atlas (Oishi *et al.,* 2011). Typically, between 6 and 12 square ROIs were defined for each white matter structure in axial

view, sizes of which were 3 × 3 × 1 voxels, or 2 x 2 x 1 voxels depending on the white matter region. Several ROIs were used for each white matter region in order to reduce the effects of differences in individual ROI placement. Next, the coordinates were mapped from standard to native space using the affine transformation matrices derived by registering each subject's T_2-weighted EPI volume to MNI standard space. The placement of the ROIs in individual images was then checked manually to ensure minimal contribution of grey matter and CSF signal to the ⟨D⟩ and FA measurements. To ensure unbiased measurements of ⟨D⟩ and FA, all ROI were defined on the T_2-weighted EPI volumes (Bozzali & Cherubini, 2007) by an investigator blind to each subjects' clinical status. Values for ⟨D⟩ and FA were then obtained for each square ROI and averaged to give mean values for each white matter structure-of-interest. Finally, blinded to the original ROI selection, the investigator also performed an assessment of intra-rater reliability of ROI placement by repeating the above analysis in 10 subjects (5 patients and 5 controls) chosen at random from the study cohort.

Based on previous studies, a set of white matter structures that are potentially affected in ALS were chosen for investigation (Abrahams *et al.,* 2005; Sarro *et al.,* 2011). These included major white matter fibre bundles of the anterior thalamic radiation, uncinate fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus, corticospinal tract, as well as the genu and splenium of corpus callosum. Also measured were the anterior cingulum, as well as the cingulum and ventral cingulum bundle connected to the hippocampus. White matter underlying sub-regions of prefrontal cortex were investigated; a) superior frontal gyrus white matter (near cortical area BA10), b) middle frontal gyrus white matter (near cortical area BA9/46), and c) inferior frontal gyrus white matter (near cortical area BA44/45). In addition, white matter within the corona radiata (superior and posterior regions), anterior corona radiata, superior parietal lobule, and temporal gyri (superior, middle and inferior) were also measured. Finally, areas that were not expected to be implicated in ALS were included namely the optic radiation and white matter within occipital gyri.

(Insert Figures 4 and 5 about here)

Corpus Callosum segmentation

As abnormalities in corpus callosum structural integrity have been shown to be a consistent feature of cerebral pathology in ALS (Yamauchi et al., 1995; Filippini et al., 2010), the corpus callosum was extracted at midline using an automatic segmentation tool (see Figure 5). Briefly, the method takes the FA and principal eigenvector volumes and registers them to the JHU-ICBM 2 mm FA template (Johns Hopkins University, Baltimore, MD, USA; http://cmrm.med.jhmi.edu) using affine registration to ensure the midline is in the centre of the x-axis. The midline corpus callosum is then identified by applying a threshold between 0.2 and 0.4 to the FA volume, and identifying those voxels whose principal eigenvectors have a predominantly left-right orientation (red) from the red/green/blue principal eigenvector colour map. The resulting segmentation mask is then applied to the $\langle D \rangle$ and FA volumes to provide average values for these water diffusion biomarkers in this structure-of -interest.

Statistical Analyses

The cognitive data were explored for normal distribution using histograms, boxplots and the Shapiro-Wilk's test of normality. In addition, all variables were checked for homogeneity of variance. Comparative group analyses of demographic and cognitive data were performed using t-tests in normally distributed data, Mann-Whitney U tests in populations that were not normally distributed, and Chi Square test for categorical variables. The one-tailed probability level was adopted for tests with a predicted directional result. White matter ROI data were analysed with univariate analysis of variance with age entered as a covariate (ANCOVA; Agosta *et al.,* 2010), and multiple comparisons were controlled for by applying a false discovery rate algorithm to the data (Pike, 2011; Sarro *et al.,*

2011). Associations between performance in cognitive tests and white matter ROI data was investigated in the patient group only using Pearson's *r* correlations.

Results

Participants

Participant's demographic data are detailed in Table 1. There were no significant differences between groups on age, gender, or premorbid IQ as assessed by the WTAR. In addition, there was no difference between patients and healthy controls in their self-reported levels of anxiety and depression. All patients had a Forced Vital Capacity of greater than 70% of their predicted value.

(Insert Table 1 about here)

Background Assessment

Patient and control data for performance in the background neuropsychological tests are detailed in Table 2. The ALS patient group was significantly impaired relative to controls in Logical memory (immediate, delayed, percentage retained and recognition), forward and reverse Digit Span, Spoken Letter Fluency Test, with a tendency towards significantly increased fluency indices on the Written Letter Fluency Test. Case by case analysis revealed that 4 patients met the Strong et al. (2009) criteria for ALS with cognitive impairment (ALSci; 5th percentile or worse on at least 2 separate tests of executive functioning) based on their performance in the fluency tasks, Brixton Spatial Anticipation test, and Reverse Digit Span. Of the 4 patients who met criteria for ALSci two also displayed memory impairment. A further 3 ALS patients who did not fulfil criteria for ALSci displayed

poor memory performance. Forced Vital Capacity predicted percentage values were not associated with scores in any of the background tests.

(Insert Table 2 about here)

Experimental Tests

Processing Speed: Details of participant's performance in the processing speed tasks are shown in Table 3. Patients and controls performed comparably in the VIT task and the RSLI task, with no significant difference observed between the groups in terms of the amount of errors made on either task.

(Insert Table 3 about here)

Dual Task: Details of participant performance in the dual-task paradigm are displayed in Table 4 and Figure 6. Patients and controls performed comparably in the initial measurement of individual level in both the DDR and VIT tasks. In the Combined Single Task scores, there was no significant difference between patients and controls; $t(58) = -0.615$, $p = 0.541$, however, in the Combined Dual Task score and more crucially in the combined Dual Task Cost there were significant differences between patients and controls; [Dual Task score $t(58) = -2.289$, $p = 0.026$; Dual Task Cost $t(58) = 2.387$, $p = 0.020$]. Figure 5 demonstrates that patients exhibited a drop in performance from single to dual task that was more than twice that of controls in both subtasks. Forced Vital Capacity predicted percentage values were not associated with scores in any of the experimental tests.

(Insert Table 4 and Figure 6 about here)

MRI Regions of Interest Analyses

The intra-rater reliability analysis indicated excellent reproducibility of ROI measurements with the SD of the difference between repeated measures of ⟨D⟩ and FA being 21 $\times$ 10^{-6} mm^2/s (mean of measurements 698 $\times$ 10^{-6} mm^2/s) and 0.012 (mean 0.411), respectively. This yielded coefficients of variation of 2.9 % for both ⟨D⟩ (range 0.6 for cingulum to 6.1 % for genu) and FA (range 0.5 for superior longitudinal fasciculus to 4.4 % for frontal white matter), which compares well with values for other studies using ROI analysis (e.g. Shenkin et al. 2005).

ROI analyses are displayed in Table 5. Significant group differences were found in the following frontal tracts; the anterior cingulate (FA and ⟨D⟩), anterior thalamic radiation (FA and ⟨D⟩), and uncinate fasciculus (⟨D⟩). In addition, group differences in white matter integrity were observed in the following prefrontal regions; superior frontal gyrus white matter (FA and ⟨D⟩), inferior frontal gyrus white matter (FA and ⟨D⟩), middle frontal gyrus white matter (FA and ⟨D⟩), and anterior corona radiata (⟨D⟩). Large differences were observed in the corticospinal tract (FA and ⟨D⟩). Further significant differences were also found in temporal areas; the hippocampal portion of the cingulum (⟨D⟩), temporal gyri white matter (FA), as well as in the inferior longitudinal fasciculus (FA) and radiata (FA). Investigation of white matter integrity in posterior brain regions (occipital gyri white matter and optic radiation) revealed no group differences. Forced Vital Capacity predicted percentage values were not associated with FA or ⟨D⟩ in any white matter regions.

(Insert Table 5 about here)

Corpus callosum segmentation: ANCOVA's revealed a significant difference in FA values between patients (Mean = 0.56, SD = 0.046) and controls (Mean = 0.59, SD = 0.043); $F(1, 47) = 6.12$, $p = 0.012$, as well as $\langle D \rangle$ values between patients (Mean =780, SD = 86×10^{-6} mm^2/s) and controls (Mean = 740, SD = 61×10^{-6} mm^2/s); $F(1, 47) = 4.045$, $p = 0.050$.

Onset site

Comparative analyses were employed to investigate the effect of onset site (Bulbar vs. Limb) in all cognitive tests, and all white matter regions/tracts; there were so significant group differences in any of the measures.

MRI correlates with neuropsychological performance

Correlations were investigated in the patient group only, and in regions/tracts in which there were significant group differences. As such the reported p values are one-tailed.

Experimental measures: Combined Dual Task Cost significantly correlated with white matter integrity in middle frontal gyrus FA; $r = -0.48$, $p = 0.004$ (Figure 7), and anterior corona radiata FA; $r = -0.32$, $p = 0.040$ (Figure 8)

(Insert Figure 7 and 8 about here)

Background measures: Spoken Letter Fluency Test significantly correlated with white matter in the superior frontal gyrus $\langle D \rangle$; $r = 0.42$, $p = 0.012$, inferior frontal gyrus FA; $r = -0.40$, $p = 0.017$,

corticospinal tract FA; r = -0.43, p = 0.010, and corpus callosum FA; r = -0.35, p = 0.049 (see Figure 8). In addition, there was an association between Reverse Digit Span and white matter integrity in the hippocampal portion of the cingulate ⟨D⟩; r = -0.41, p = 0.018. Relationships between the cognitive tasks were also investigated to deduce whether there was any overlap between performance on different cognitive measures. There was no correlation between the Combined Dual Task Cost and Spoken Letter Fluency Test; r = 0.06, p = 0.745, or any of the significant cognitive measures.

Discussion

These data show that ALS patients exhibited impairments in dual task performance while processing speed remained preserved. This selective deficit indicates the presence of executive dysfunction in ALS in the absence of generic cognitive slowing. The tests employed assessed processing speed for abstract visual and verbal information by manipulating stimulus duration, and as such account for motor disability with untimed responses. Inconsistencies between these and previous studies may be a reflection of the type of tasks employed; the Trail Making Test part A (Hanagasi *et al.,* 2002) and the Digit Symbol Test (Mezzapesa *et al.,* 2007) place considerable demand on the motor (hand) functions. The current findings suggest that studies which report deficits in psychomotor speed (see Raaphorst *et al.,* 2010 meta-analysis) are most likely a reflection of motor impairment rather than cognitive slowing, and that ALS patients *are* able to process simple visual information at a normal rate. Processing speed, when isolated from motor functioning and other high-order processes, is not impaired in ALS patients and does not contribute to other observed cognitive impairments.

In contrast, ALS patient performance in the Dual Task was significantly impaired compared to controls; the accuracy cost incurred by performing two tasks concurrently was more than twice as high in patients compared to controls. The individual tasks were matched to each participant's

individual ability level so the dual task effect could not be the result of single task difficulty (Anderson *et al.*, 2011). This was confirmed by similar accuracy scores achieved by patients and controls in both Single Task conditions. Furthermore, patients and controls showed no difference in terms of the Individual ability levels on each task and so were able to perform as well as controls. Thus, the dual task decrement exhibited by patients is likely to be a reflection of a specific impairment in the ability to co-ordinate cognitive resources appropriately between the two tasks, and reflect dysfunction of the central executive. Dual task impairments are observed in Alzheimer's Disease (Logie *et al.,* 2004; MacPherson *et al.,* 2007) and have also been reported to a lesser extent in FTD (Perry & Hodges, 2000; Sebastian & Hernandez-Gill, 2010) and in a previous study of ALS based on reaction time measures (Schreiber *et al.,* 2005). The current investigation employed a preload methodology to minimise motor demands (Cocchini *et al.,* 2002), and constituent tasks for which accuracy was the outcome measure, and as such is the first demonstration of a dual task impairment in ALS that it independent of single task difficulty, processing speed, and motor functioning.

Dual task performance correlated with FA values in middle frontal gyrus white matter and corona radiata, whereby poor performance was associated with lower white matter integrity. The middle frontal gyrus (or dorsolateral prefrontal cortex) is thought to be highly influential in the regulation of executive processes such as strategy formation, set-shifting and working memory (Stuss, 2002; Royall *et al.,* 2002) and was previously identified as a site of dysfunction in ALS in functional imaging (Abrahams *et al.* 1996; 2004). The white matter regions identified by the current study correspond well to the prefrontal areas that were suggested to reflect central executive activity in functional imaging studies of dual tasking in healthy adults (D'Esposito *et al.,* 1995; Wager & Smith, 2003). The neural correlates of dual tasking are hotly debated (Erickson *et al.,* 2005), however, functional imaging studies have demonstrated the importance of the bilateral frontal gyri (including the

dorsolateral prefrontal cortex) in managing and coordinating response selection and interference (MacDonald *et al.,* 2000; Wager & Smith, 2003), and it is possible that the white matter findings presented in this study underpin dysfunction in these processes. It has also been suggested that executive functioning is best understood in terms of interactions between networks of regions (Collette & Van der Linden, 2002), and that dual tasks impose higher processing demands on cortical areas already involved in the component single tasks. Thus, it is also possible that the correlation with white matter underlying dorsolateral prefrontal cortex may be a reflection of the high demands on working memory that are required to maintain performance on the DDR task whilst completing a concurrent task.

Of particular interest is the finding that performance on the Dual task was associated with different white matter pathways than the commonly reported letter fluency deficits. The finding of letter fluency deficits is consistent with numerous others studies reporting this as a striking feature of the cognitive profile of ALS (e.g. Moretti *et al.,* 2002; Lomen-Hoerth *et al.,* 2003; Abrahams *et al.,* 2004), confirming that verbal fluency impairments are one of the core deficits that characterize cognitive change in ALS. Longer fluency index times in the Spoken Letter Fluency Test were associated with reduced FA in white matter in the inferior frontal gyrus (adjacent to Broca's/Brodmann area 44), superior frontal gyrus (adjacent to Brodmann area 10), corpus callosum, and corticospinal tract but not the middle frontal gyrus. These findings are generally consistent with a previous study showing that ALS patients with impaired verbal fluency had reduced white matter volumes within the superior and medial frontal lobes (Abrahams *et al.,* 2005), but, moreover, further builds on these findings to demonstrate firstly a direct correlation and secondly changes in integrity of specific structural pathways. The white matter correlates of verbal fluency performance identified by the current study are also concordant with functional imaging studies in ALS which have shown decreased blood-oxygen response in both the anterior prefrontal cortex (Brodmann Area 10) and

inferior frontal gyrus (Brodmann Area 44) in response to fluency tasks (Abrahams *et al.* 2004). Studies in healthy participants of fluency have also highlighted the importance of a prefrontal network including Broca's Area and left inferior frontal gyrus (Abrahams *et al.* 2003; Hirshorn & Thompson-Schill, 2006). Furthermore, this region has been noted as a site of pathological focus in patients with ALS-Aphasia syndrome (Bak *et al.* 2001). The correspondence between studies suggests that disruption to these white matter pathways particularly in the inferior frontal gyrus may underpin the cognitive changes observed in ALS patients with impaired verbal fluency.

The correlation between verbal fluency and white matter integrity in the corpus callosum also highlights this area as sensitive to cognitive change in ALS patients. Previous ALS studies have indicated some association between reduced corpus callosum integrity and cognitive impairment (Yamauchi *et al.,* 1995; Abrahams *et al.,* 2005), with the former study suggesting that pathology in the *anterior* portion of this structure was associated with cognitive and behavioural changes. The methods employed by the current study were unable to differentiate between discrete portions of the corpus callosum, although the trend toward low FA in the genu, but not splenium, may indicate the presence of an anterior gradient of corpus callosum involvement as postulated by others (Filippini *et al.,* 2010). Indeed, corpus callosum changes have been reported in DTI studies of FTD (Matsuo *et al.,* 2008) suggesting that this structure may be influential in the cognitive changes that characterise this disorder, further highlighting the pathological link between ALS and FTD.

The observed correlation between verbal fluency performance and corticospinal tract integrity suggests that fluency performance may be sensitive to disease severity. This may be related to the propensity for patients with bulbar onset to show more upper motor neuron degeneration, as well as being more likely to exhibit cognitive impairment (Abrahams *et al.,* 1997), although other studies

have suggested that cognitive impairment occurs early in the disease and does not progress at the same rate as motor dysfunction (Schreiber *et al.,* 2005).

Thus, performance in these two tests of executive functioning appears to be underpinned by different white matter pathways within the prefrontal cortex. Moreover, Dual-task and Verbal Fluency performance were highly uncorrelated with each other, suggesting that impairments in executive functions are indeed dissociable in ALS patients. Further support for this proposal is provided by research which postulates that executive functions are dissociable at a behavioural and neuroanatomical level (Goldman-Rakic, 1995; Jurado & Roselli, 2007), and particularly by studies which suggest that verbal fluency and dual tasking do not share the same cognitive processes, making them less likely to rely on the same neural pathways (Miyake *et al.,* 2000).

Patients also exhibited impairment in the digit span measures, indicative of a deficit in working memory which has been reported in other studies (Rackowicz *et al.,* 1998; Abrahams *et al.,* 2000). A correlation was observed between performance on the Reverse Digit Span task and increased ⟨D⟩ in the hippocampal portion of the cingulum. The hippocampal portion of the cingulum is traditionally associated with episodic and long-term memory (Kohler *et al.,* 1998), indeed it has been shown to correlate with cognitive functioning in Alzheimer's disease (Nakata *et al.,* 2009). In the present study in addition to executive dysfunction, memory impairment was detected. Memory dysfunction in ALS has been previously highlighted (Raaphorst et al. 2010), although typically related to secondary executive retrieval dysfunction. Here the patient sample showed deficits not only in measures of immediate memory, but also in retention and recognition, and as such are unlikely to be explained through an executive dysfunction route alone. This suggests a primary memory deficit in some ALS patients. Increasingly however, the hippocampus has been shown to have a role in working memory

paradigms (Ranganath & D'Esposito, 2002), and together with the posterior cingulate has been associated with tasks assessing multiple cognitive domains suggesting that it may be a crucial structure in complex cognitive circuitry (Kantarci *et al.,* 2011). Moreover, neuropathological studies in ALS patients with and without dementia have shown abnormalities in the hippocampus (Okamoto *et al.,* 1991; Takeda *et al.,* 2009).

The current study employed a prevalent sampling method, and as a result included a small number of patients (n=2) with disease duration of over five years, although patients with significant respiratory dysfunction were excluded. Large population studies of cognitive impairment in ALS using incidence sampling methods have shown similar rates of impairment as those from prevalent samples, but they have also revealed a more heterogeneous presentation not only of executive dysfunction but including changes in language and memory (Phukan et al. 2011, Goldstein and Abrahams, 2013). Although there was no evidence of language dysfunction (given that only one naming test was performed), memory dysfunction was present which is consistent with the findings from incident samples (Phukan et al. 2011).

The white matter ROI analyses revealed extensive changes in structural integrity in ALS patients relative to controls. Reduced structural integrity was found in the uncinate fasciculus which connects the temporal lobes and amygdala to orbitofrontal and inferior regions of the prefrontal lobes, a result which is consistent with other studies in ALS (Sato *et al.,* 2010; Agosta *et al.,* 2010) and FTD (Matsuo *et al.,* 2008). Further changes were shown in the patient group in white matter underlying the superior, middle, and inferior frontal gyri, as well as in the temporal gyri. In addition, changes were evident in the anterior thalamic radiation which connects the thalamus to areas of the prefrontal cortex, as well as in the anterior and hippocampal portions of the cingulum, which

connects subcallosal regions to the hippocampus and frontal lobes respectively. The observed changes in prefrontal associative fibres and cingulum are largely consistent with those indicated by a previous study showing volumetric white matter reductions in ALS patients using less refined automated volumetric estimations (Abrahams *et al.,* 2005). In agreement with other studies (Abrahams *et al.,* 2005; Filippini *et al.,* 2010), reduced structural integrity was observed in the corpus callosum, as well as corticospinal tract, indicative of upper motor neuron pathology which has been consistently shown in previous DTI investigations (Abe *et al.,* 2004; Ciccarelli *et al.,* 2006; Agosta *et al.,* 2010). Concordant with a recent DTI investigation (Sarro *et al.,* 2011), ALS patients showed reduced structural integrity in the inferior longitudinal fasciculus, one of the long association bundles connecting the temporal and occipital lobes. The DTI data from the current study lends support to the postulated continuum between classical ALS and FTD (Lomen-Hoerth *et al.,* 2003; Abrahams *et al.,* 2004; Murphy *et al.,* 2007; Sage *et al.,* 2007; Raaphorst *et al.,* 2010), as it highlights a preponderance for frontotemporal white matter pathology which may play a crucial role in the multi-system involvement observed in this disorder.

In summary, the findings of the current study show a pattern of cognitive impairment in ALS with predominant executive dysfunction characterised by a deficit in the central executive with no slowing of processing speed. Moreover impairments in different types of executive functions correlated with white matter integrity in distinct prefrontal pathways, with dual task impairment associated with dysfunction of middle frontal gyrus, while letter fluency deficits appear more dependent on the superior and inferior gyri and corpus callosum. Whether such deficits occur at different stages of disease and whether they may be used as tools to map out cerebral spread of the disease may be of a matter for future investigation.

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Table 1.Demographic data for patients and controls.

	n (ALS:HC)	ALS Patients	Healthy Controls	*t or U or X^2*	*P value*
Age (years)	30:30	58.5 (28 – 79)	59.1 (34 – 79)	-0.203	0.840
Gender (M:F)	30:30	17:13	17:13	0.00	1.000
WTAR IQ	27:30	104 (81 – 123)	108 (87 – 124)	-1.524	0.133
HADS A	29:30	7 (0 – 19)	5.4 (0 – 14)	-1.112	0.266
HADS D	29:30	3 (0 – 9)	3.1 (0 – 10)	0.016	0.988
Disease Duration (months)	30:0	19.5 (5 – 88)	----------	----------	----------
ALSFRS –R	30:0	38.8 (21 – 47)	----------	----------	----------
FVC % Pred.	30:0	99.3 (70.2 – 155.3)	----------	----------	----------

Mean values with ranges in parentheses are presented. A median value is presented for disease duration (two patients were included with disease duration of over 60 months). Ratios are presented for number of patients versus controls in each task and for group gender breakdown. WTAR = Wechsler Test of Adult Reading, HADS A = Hospital Anxiety and Depression Scale - Anxiety, HADS D = Hospital Anxiety and Depression Scale – Depression, ALSFRS-R= Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised, FVC % Pred. = Forced Vital Capacity percentage of predicted value, M = male, F = female

Table 2. Background neuropsychological test data for patients and controls*.

	n (ALS:HC)	ALS Patients	Healthy Controls	*t or U*	*P value*
Log Memory Imm.	29:30	23.1 [7.4]	27.8 [7.9]	-2.367	**0.021**
Log Memory Del.	29:30	18.2 [7.4]	24.7 [8.1]	-3.184	**0.002**
Log Memory % Delay	29:30	76.0 [23.0]	87.2 [11.1]	2.344	**0.019**
Log Memory Rec.	29:30	24.9 [2.6]	26.3 [2.8]	2.181	**0.029**
Graded Naming Test	26:29	23.8 [4.1]	25.0 [3.4]	-1.077	0.282
Spatial Span Fwd	27:30	5.7 [1.1]	5.5 [0.9]	0.615	0.539
Spatial Span Rev	27:30	4.9 [1.2]	4.7 [1.1]	0.391	0.696
Digit Span Fwd	27:29	6.8 [1.2]	7.4 [1.0]	-2.078	**0.038**
Digit Span Rev	27:29	5.0 [1.0]	5.6 [1.2]	-2.084	**0.037**
Brixton Errors	27:30	16.8 [7.8]	14.5 [7.4]	1.355	0.175
Spoken Letter Fluency Test (*fi*)	29:30	4.9 [2.8]	3.2 [1.0]	3.048	**0.002**
Written Letter Fluency Test (*fi*)†	16:30	9.5 [4.6]	7.4 [3.6]	1.730	0.084

Mean values with standard deviations in parentheses are presented. * Significant results are highlighted in bold. † 14 ALS patients were unable to write effectively due to ALS disability. Ratios are presented for number of patients versus controls in each task. Fwd = Forward, Rev. = Reverse, Log. = Logical, Imm. = Immediate recall, Del. = Delayed recall, % Delay = Percentage of information recalled at delay compared to immediate condition, Rec. = Recognition, *fi* = fluency index.

Table 3. Processing speed data for ALS patients and controls.

	n (ALS:HC)	ALS Patients	Healthy Controls	*t*	*p value*
VIT (errors)	25:29	13.5 [8.0]	12.9 [7.6]	0.565	0.572
RSLI (errors)	28:30	16.4 [3.9]	15.8 [3.1]	0.648	0.520

Mean values with standard deviations in parentheses are presented. Ratios are presented for number of patients versus controls in each task. VIT = Visual Inspection Time, RSLI = Rapid Serial Letter Identification

Table 4. Dual task performance for ALS patients and controls*.

	n (ALS:HC)	ALS Patients	Healthy Controls	*t or U*	*P value*
DDR Individual Level	30:30	5.4 [1.2]	5.8 [1.0]	-1.385	0.166
VIT Individual Level	30:30	62.2 [24.6]	62.3 [18.6]	-0.446	0.656
Combined Single Task (% correct)	30:30	92.6 [6.7]	93.6 [5.0]	-0.615	0.541
Combined Dual Task (% correct)	30:30	85.7 [9.6]	90.8 [7.0]	-2.289	**0.026**
Combined Dual-Task Cost (% change)	30:30	7.2 [7.2]	2.5 [7.7]	2.387	**0.020**

Mean values with standard deviations in parentheses are presented. * Significant results are highlighted in bold. Ratios are presented for number of patients versus controls in each task. VIT = Visual Inspection Time, DDR = Delayed Digit Recall

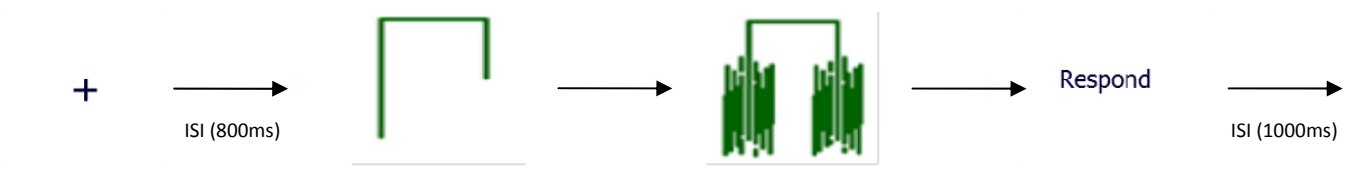
Table 5. White matter ROI mean measurements and comparison between ALS patients and controls.*

	ALS Patients	**Healthy Controls**	***t or U***	***P value***	***FDR adj.***
Anterior Cingulum FA	0.41 [0.055]	.45 [0.063]	-3.105	0.013	**0.014**
Anterior Cingulum ⟨D⟩†	670 [66]	630 [62]	2.706	0.013	**0.014**
Atr FA	0.46 [0.039]	0.49 [0.037]	-3.028	0.002	**0.004**
Atr ⟨D⟩†	670 [56]	630 [37]	2.795	0.001	**0.003**
SFG white matter FA	0.28 [0.036]	0.30 [0.033]	-2.371	0.019	**0.016**
SFG white matter ⟨D⟩†	780 [73]	740 [46]	2.336	0.010	**0.014**
IFG white matter FA	0.36 [0.047]	0.38 [0.029]	-1.981	0.013	**0.014**
IFG white matter ⟨D⟩†	690 [51]	670 [38]	1.983	0.025	**0.018**
MFG white matter FA	0.28 [0.040]	0.31 [0.041]	-2.336	0.013	**0.014**
MFG white matter ⟨D⟩†	740 [61]	710 [53]	1.981	0.059	**0.038**
A-CR FA	0.27 [0.040]	0.30 [0.035]	-3.246	0.001	**0.003**
A-CR ⟨D⟩†	810 [82]	770 [54]	1.759	0.021	**0.016**
Genu FA	0.42 [0.070]	0.45 [0.069]	-1.353	0.151	0.079
Genu ⟨D⟩†	1070 [180]	1030 [160]	.932	0.305	0.120
Uncinate fas. FA	0.40 [0.051]	0.42 [0.054]	-1.457	0.119	0.070
Uncinate fas. ⟨D⟩†	700 [42]	680 [39]	2.296	0.018	**0.016**
Cingulum FA	0.45 [0.077]	0.47 [0.078]	-1.079	0.332	0.127
Cingulum ⟨D⟩†	650 [81]	630 [72]	1.434	0.194	0.088
H-Cg FA	0.29 [0.040]	0.31 [0.036]	-1.500	0.124	0.070
H-Cg ⟨D⟩†	720 [78]	680 [57]	3.075	0.021	**0.016**
Cst FA	0.53 [0.039]	0.57 [0.036]	-4.354	0.000	**0.000**

Cst ⟨D⟩†	650 [37]	630 [29]	3.282	0.002	**0.004**
Ilf FA	0.42 [0.030]	0.44 [0.029]	-2.765	0.006	**0.011**
Ilf ⟨D⟩†	720 [46]	710 [38]	0.872	0.176	0.088
Slf FA	0.46 [0.042]	0.48 [0.044]	-1.079	0.283	0.117
Slf ⟨D⟩†	640 [41]	630 [33]	0.946	0.287	0.117
SPL white matter FA	0.39 [0.038]	0.40 [0.037]	-0.917	0.103	0.064
SPL white matter ⟨D⟩†	690 [41]	680 [41]	0.402	0.631	0.216
Splenium FA	0.57 [0.062]	0.59 [0.064]	-1.100	0.197	0.088
Splenium ⟨D⟩†	760 [91]	770 [110]	-0.030	0.879	0.286
TG white matter FA	0.31 [0.033]	0.34 [0.025]	-3.527	0.001	**0.003**
TG white matter ⟨D⟩†	750 [57]	730 [50]	1.656	0.056	**0.038**
Corona Radiata FA	0.34 [0.045]	0.36 [0.035]	-2.336	0.021	**0.016**
Corona Radiata ⟨D⟩†	660 [41]	650 [58]	2.099	0.254	0.110
OG white matter FA	0.39 [0.033]	0.39 [0.044]	0.591	0.589	0.207
OG white matter ⟨D⟩†	750 [74]	750 [75]	-0.266	0.781	0.260
Optic Radiation FA	0.42 [0.038]	0.41 [0.039]	1.353	0.189	0.088
Optic Radiation ⟨D⟩†	740 [51]	730 [56]	0.636	0.585	0.207

Mean values with standard deviations in parentheses are presented. * Significant results are highlighted in bold. † values x 10^{-6} mm^2/s. Atr = Anterior Thalamic Radiation, A-CR = Anterior Corona Radiata, SFG = Superior Frontal Gyrus, IFG = Inferior Frontal Gyrus, MFG = Middle Frontal Gyrus, H-Cg = Hippocampal portion of the Cingulum, Cst = Corticospinal Tract, Ilf = Inferior Longitudinal Fasciculus, Slf = Superior Longitudinal Fasciculus, SPL = Superior Parietal Lobule, TG = Temporal Gyri, OG = Occipital Gyri, FA = Fractional Anisotrophy, ⟨D⟩ = Mean Diffusivity. FDR adj = p values after adjustment for False Discovery Rate.

Figure list.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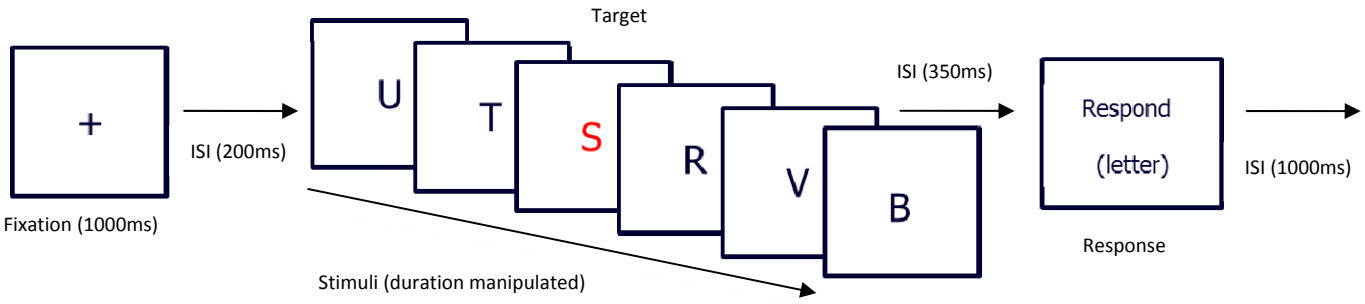
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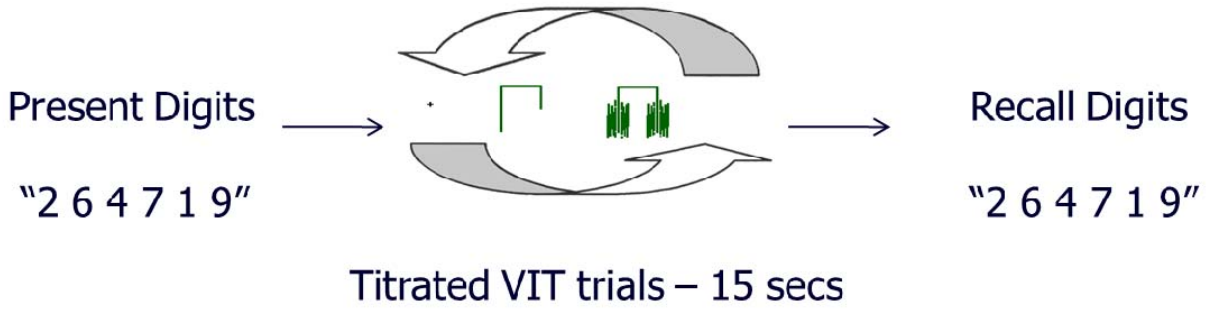

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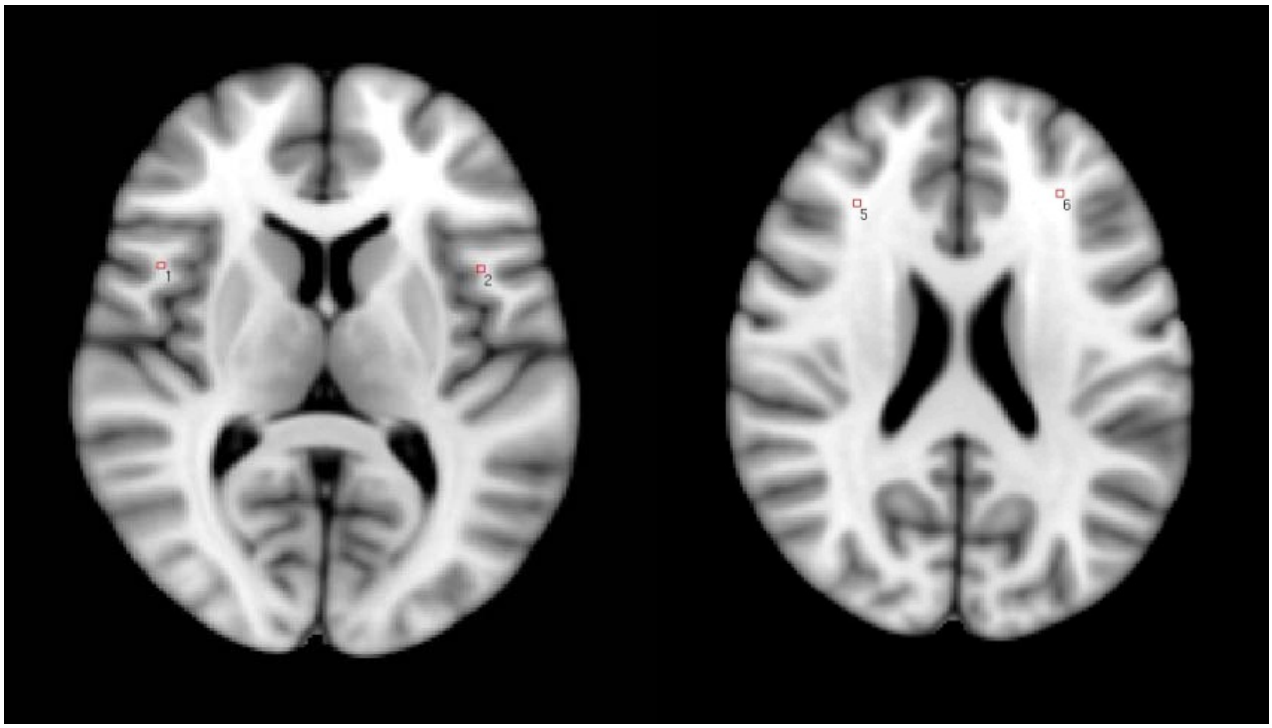
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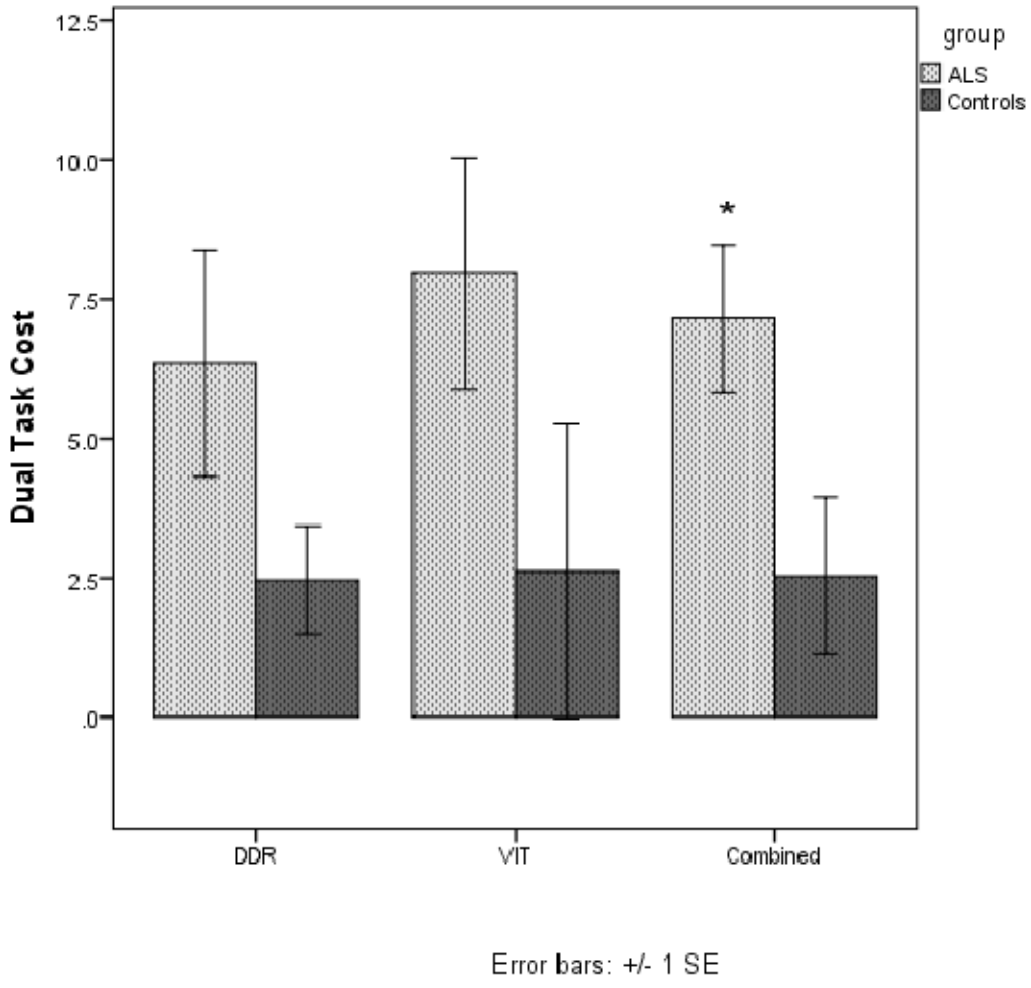
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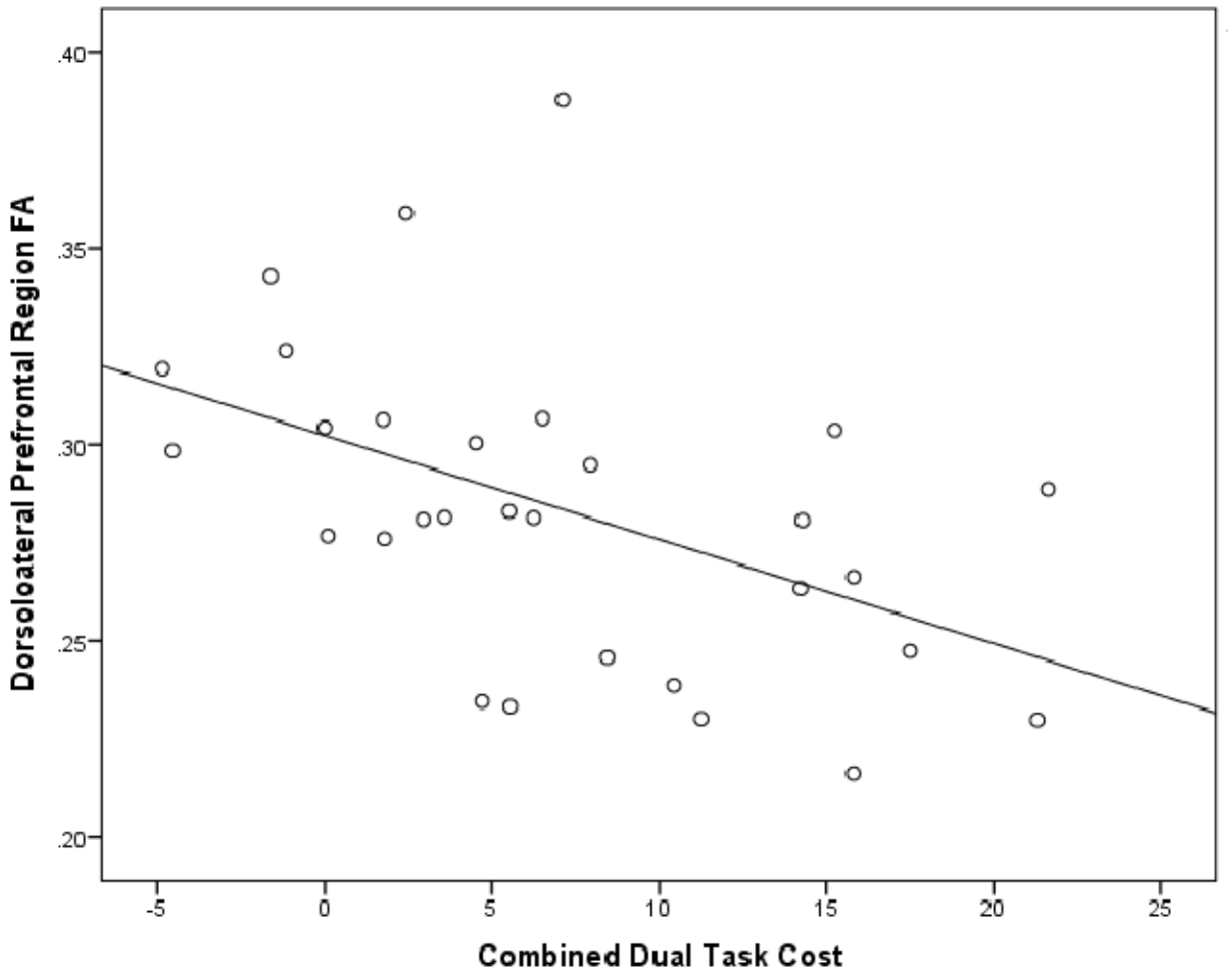
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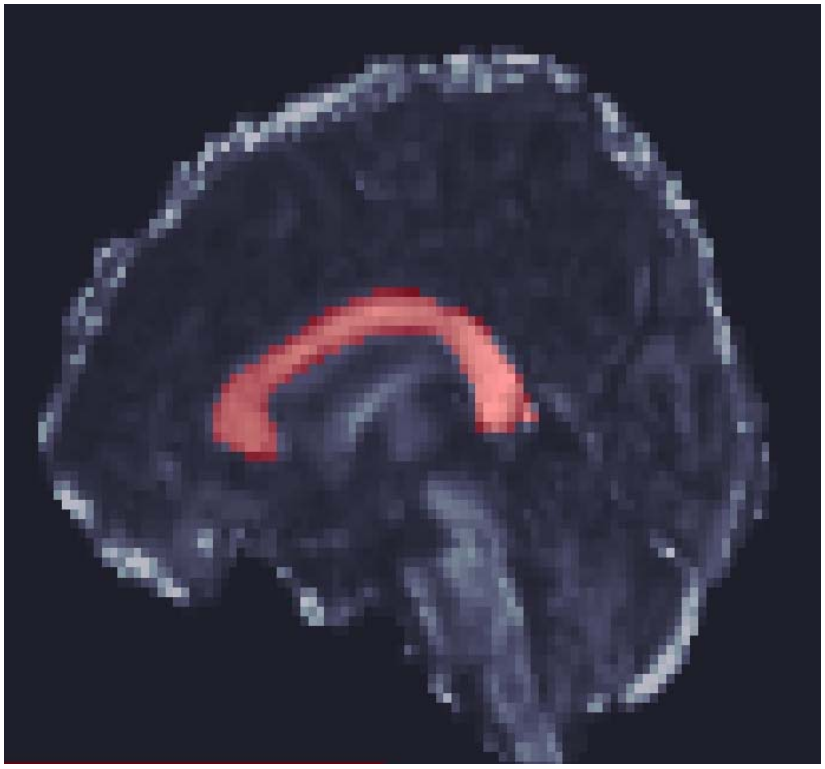

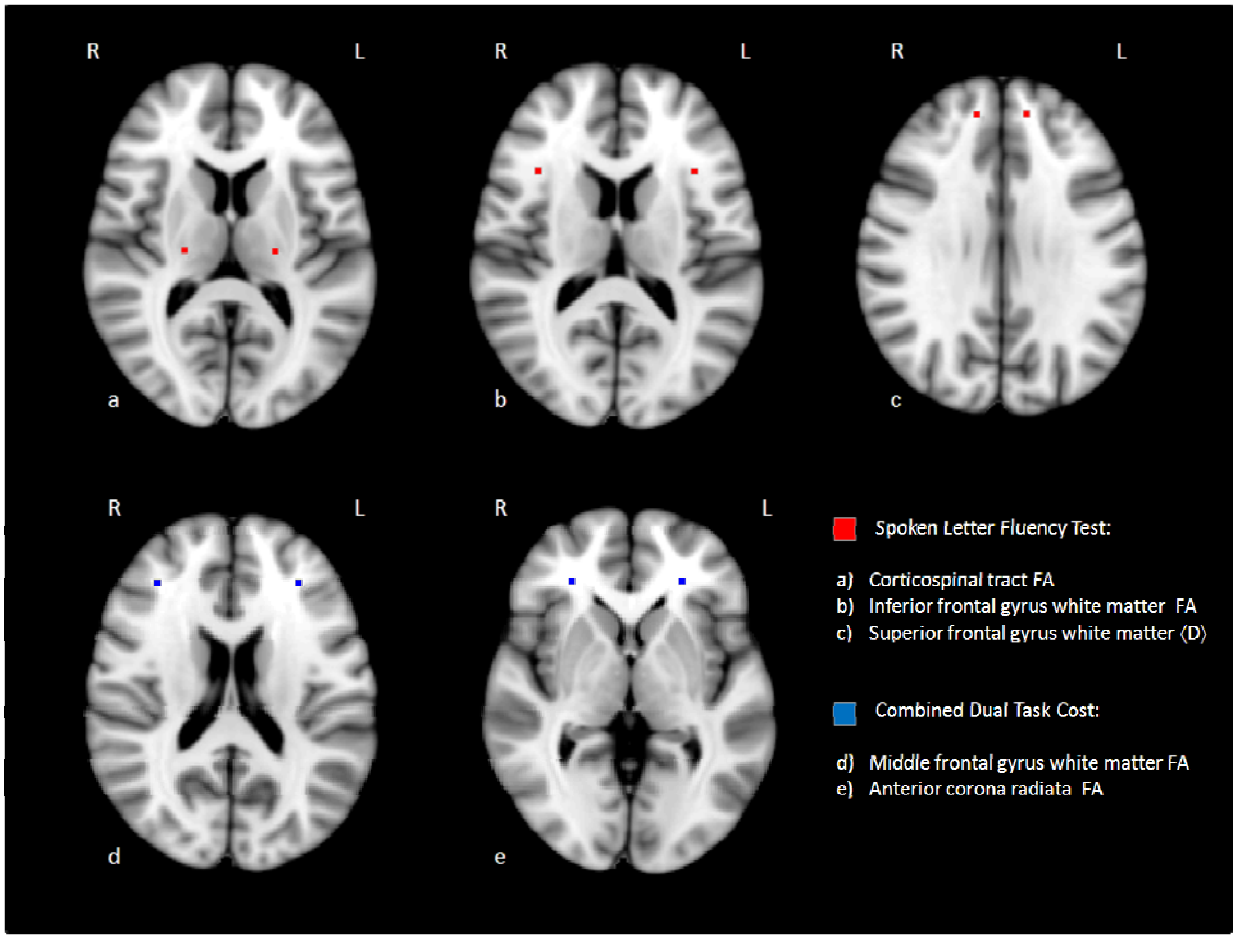

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